ESA Therapy

Hussein Sheashaa, MD, FACP

Professor of Nephrology, Urology and Nephrology Center and Director of Medical E-Learning Unit, Mansoura University and Executive Director of ESNT-Virtual Academy: http://lms.mans.edu.eg/esnt/

Mansoura, MNDU, 12.11.2015

Urology and Nephrology Center

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Key Points

- Introduction
- ESA Types
- ESA route
- Cost
- Hemoglobin target
- ESA and CKD progression

Anemia Management: Cohort (951 ND-CKD2-5)

Urology and Nephrology Center

Original Article

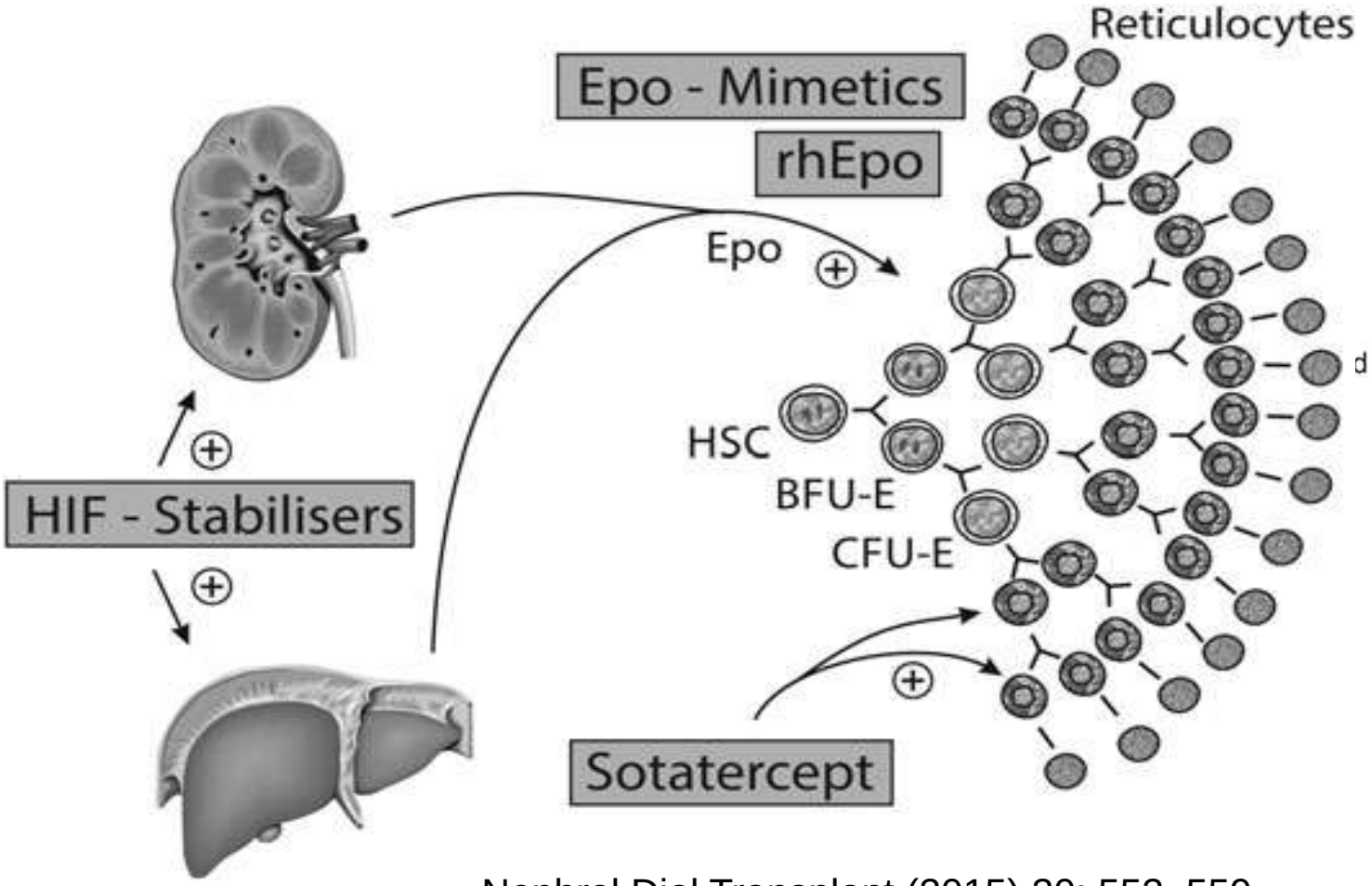
Anaemia management and mortality risk in newly visiting patients with chronic kidney disease in Japan: The CKD-ROUTE study

SOICHIRO IIMORI,[1] SHOTARO NAITO,[1] YUMI NODA,[2] HIDENORI NISHIDA,[3] HIROMI KIHIRA,[4] NAOFUMI YUI,[1] TOMOKAZU OKADO,[1] SEI SASAKI,[1] SHINICHI UCHIDA[1] and TATEMITSU RAI[1]

[1]Department of Nephrology, Tokyo Medical and Dental University, [2]Department of Nephrology, Nakano General Hospital, [4]Department of Nephrology, Tokyo Metropolitan Tama Medical Center, Tokyo, and [3]Department of Nephrology, Hiratsuka Kyosai Hospital, Kanagawa, Japan

Nephrology ***20 (2015) 601–608***

Current ESAs



Nephrol Dial Transplant (2015) 30: 553–559

New Strategies: Stimulate Erythropoiesis

Not Directly Targeting the EPO

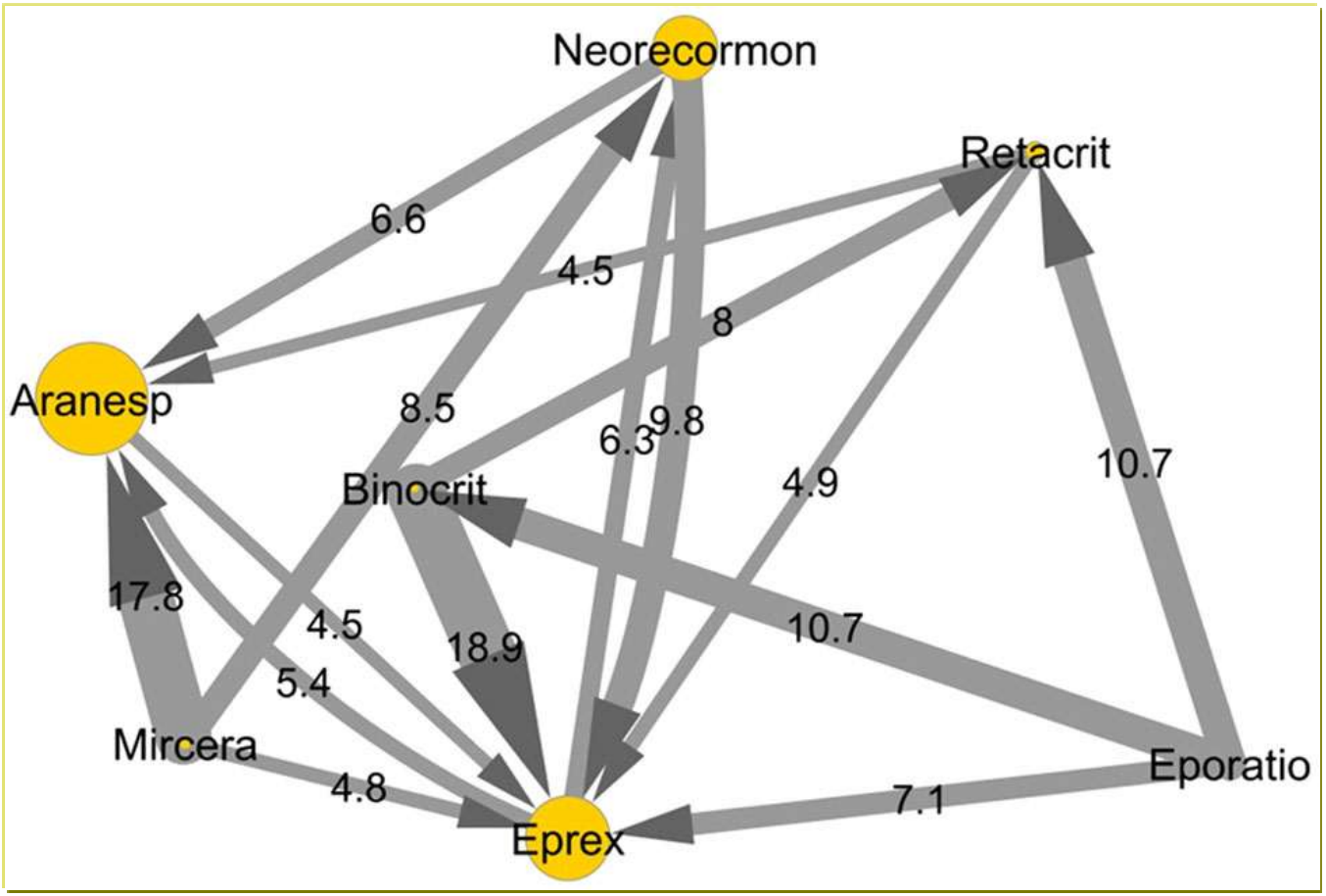
- HIF stabilizers
  - FG-4592 (Roxadustat)
  - AKB-6548
  - GSK1278863
  - BAY 85-3934 (Molidustat)
  - JTZ-951
  - DS-1093a
- Activin traps
  - Sotatercept (ACE-011)
  - Luspatercept (ACE-536)
  - LY2157299

Targeting the EPO Receptor

- EPO mimetic peptides
  - Centocor molecules: CNTO 528, CNTO 530, CNTO 531
  - AplaGen GmbH: AGEM400(HES)
  - Peginesatide[a]
- EPO fusion proteins
  - EPO-EPO dimers
  - EPO-CPT
  - EPO-$(CPT)_3$
  - Albumin-EPO
  - EPO-hyFc (Genexine GX-E2)
- Antibody agonists to EPO receptor
  - Mouse monoclonal IgG
  - Ab12 molecule
  - Ab12.6 (Abbott Laboratories ABT-007) molecule
- EPO gene therapy (TARGT EPO)
- Dimerization of EPO receptor intracellular domain with a CID

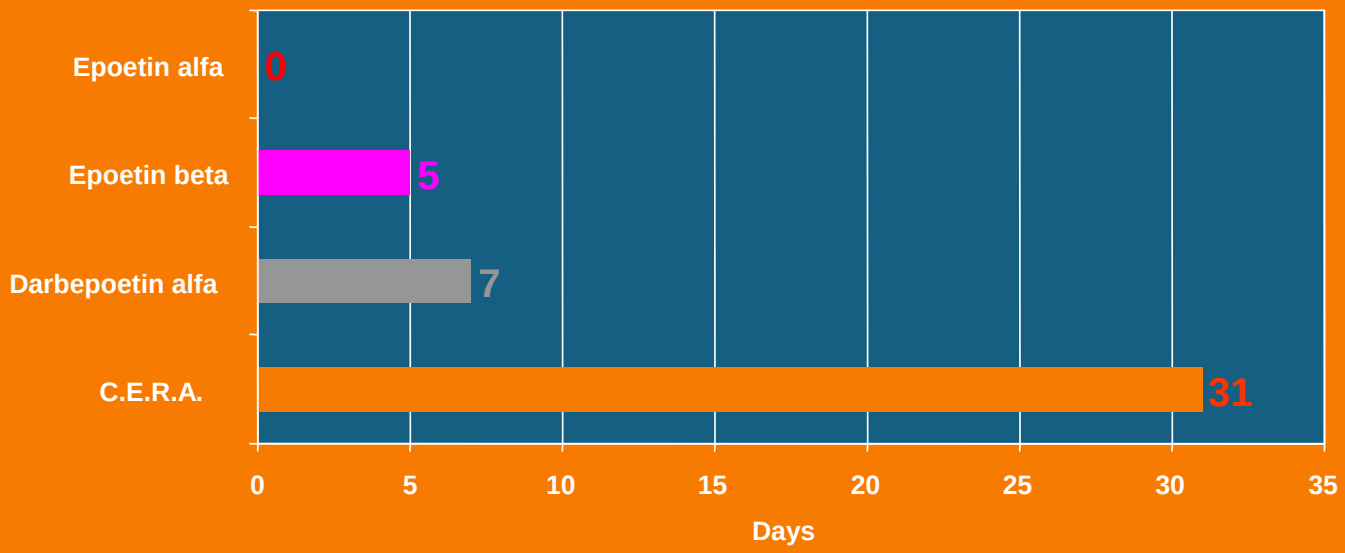
Am J Kidney Dis. 2015; in press

ESA Therapy:
Switch



BioDrugs (2015) 29:275–284

ESA Therapy:
Refrigeration



ESA Initiation

Agent	Recommended Dose
Epoetin	50-100 units/kg administered either IV or SC, 3 times per week

Prof. Sobh Courtesy

Conversion Among ESA

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Estimated Aranesp Starting Doses (mcg/week) for Patients With CKD on Dialysis Based on Previous Epoetin alfa Dose (Units/week)

Previous Weekly Epoetin alfa Dose (Units/week)	Aranesp Dose (mcg/week)	
	Adult	Pediatric
< 1,500	6.25	*
1,500 to 2,499	6.25	6.25
2,500 to 4,999	12.5	10
5,000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
≥ 90,000	200	200

*For pediatric patients receiving a weekly epoetin alfa dose of < 1,500 Units/week, the available data are insufficient to determine an Aranesp conversion dose.

MIRCERA dose when converting from another ESA

Previous Weekly Darbepoetin Alfa Dose (µg/week)	Previous Weekly Epoetin Dose (Units/week)	MIRCERA Starting Dose (µg/month)
< 40	< 8000	120
40-80	8000-16000	200
> 80	> 16000	360

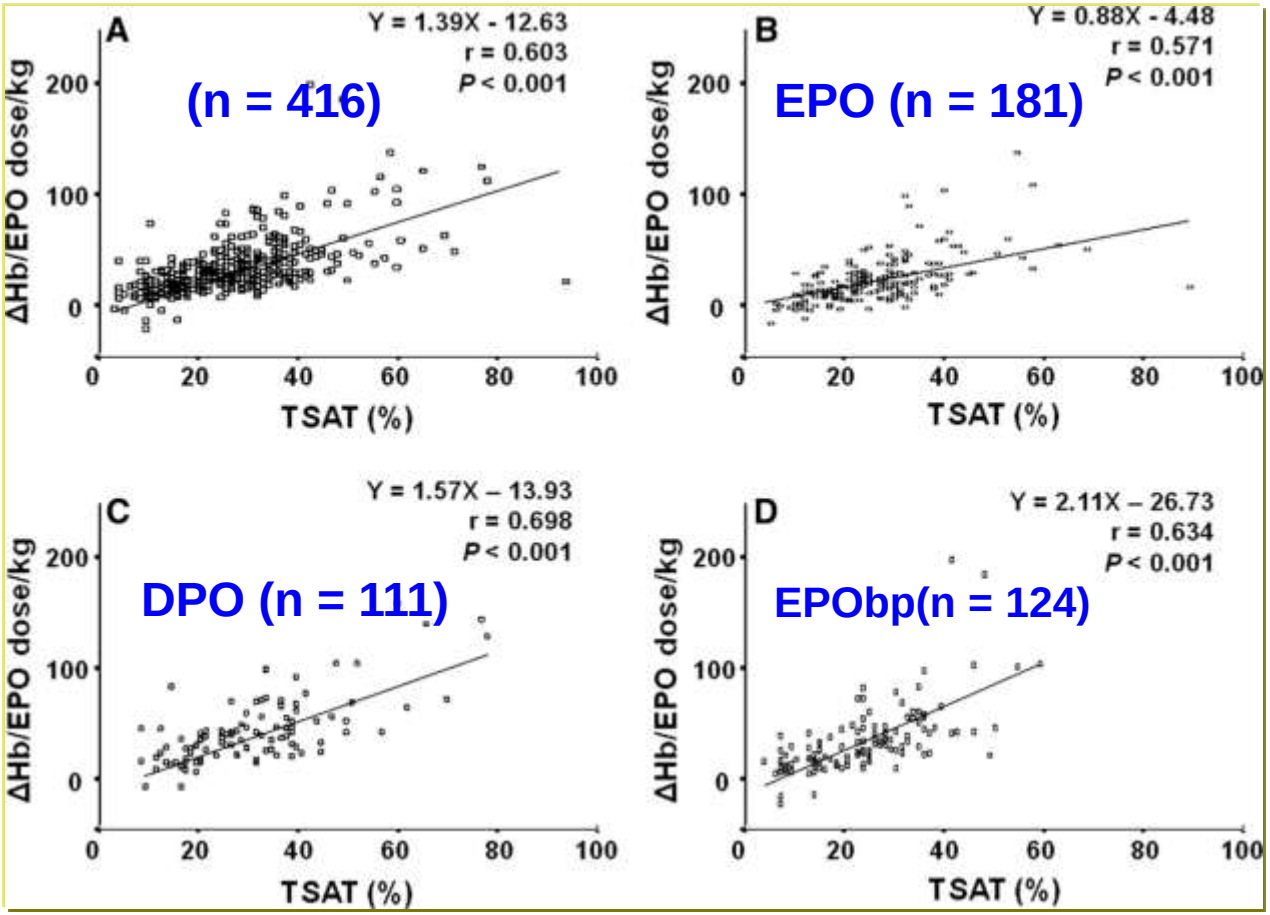
ESA Therapy:
Suggested Contraindications

Suggested contraindications for the use of rHuEPO.

1. Previous history of thrombotic vascular event (in past 6 months) (MI/CVA/TIA/DVT/PE)
2. Previous history of seizure
3. Uncontrolled hypertension (SBP > 160 mmHg, DBP > 90 mmHg)
4. Risk factors predisposing to pre-op DVT (e.g. immobility, fractured joint)
5. Hypercoagulable disease states (e.g. positive Lupus anticoagulant)
6. Cancer Diagnosis/Treatment (in past 3 years). Not an absolute exclusion, consider each patient individually. If proceed, close monitoring and Hb not to exceed 135 g/l

Transfusion and Apheresis Science 50 (2014) 16–19

ESA Response:
Predictors of Response



Clin Exp Nephrol 2015;In press

Which ESA Therapy?

Urology and Nephrology Center

56 Studies, 15.596 Patients

[Intervention Review]

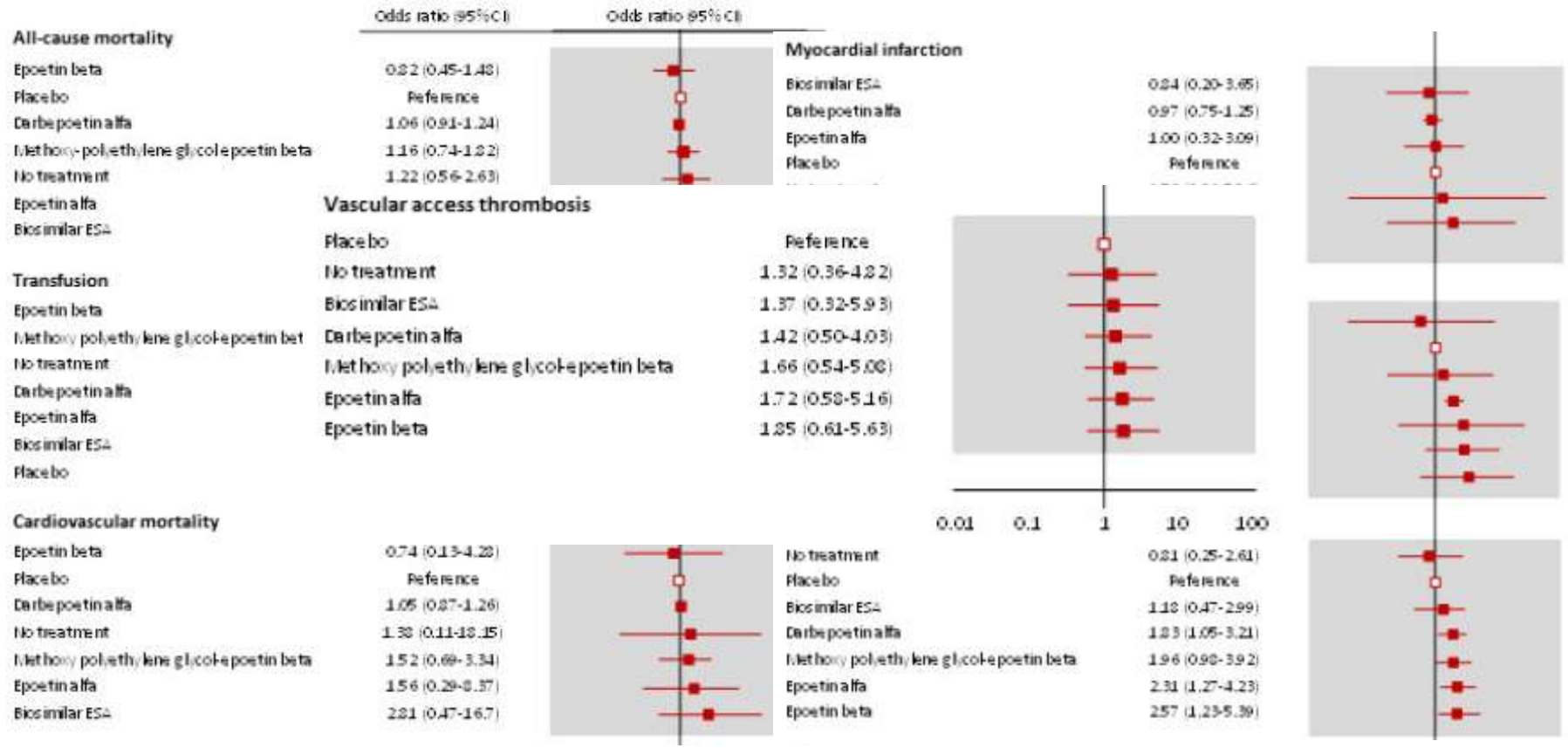
Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis

Suetonia C Palmer[1], Valeria Saglimbene[2], Dimitris Mavridis[3,4], Georgia Salanti[5], Jonathan C Craig[6,7], Marcello Tonelli[8,9], Natasha Wiebe[10], Giovanni FM Strippoli[6,7,11,12,13,14]

[1]Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand. [2]Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, Santa Maria Imbaro, Italy. [3]Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece. [4]Department of Primary Education, University of Ioannina, Ioannina, Greece. [5]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece. [6]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [7]Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [8]Department of Medicine, University of Calgary, Calgary, Canada. [9]Cumming School of Medicine, University of Calgary, Calgary, Canada. [10]Department of Medicine, University of Alberta, Edmonton, Canada. [11]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [12]Department of Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, Santa Maria Imbaro, Italy. [13]Medical-Scientific Office, Diaverum, Lund, Sweden. [14]Division of Nephrology and Transplantation, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy

The Cochrane Library 2014, Issue 12

Which ESA Therapy?



The Cochrane Library 2014, Issue 12

Hemoglobin Variability:
Effect of Different ESA

BJCP British Journal of Clinical Pharmacology
BPS BRITISH PHARMACOLOGICAL SOCIETY

Meta analysis

Between-subjects hemoglobin variability is not associated with the erythropoiesis-stimulating agent used to treat anemia in dialysis: a meta-analysis

(n 4,983)

Br J Clin Pharmacol. 2012 Jul 16.

ESA Route:
Outcome

Route of Administration	
Intravenous (*n*=57,602)	Subcutaneous (*n*=5108)

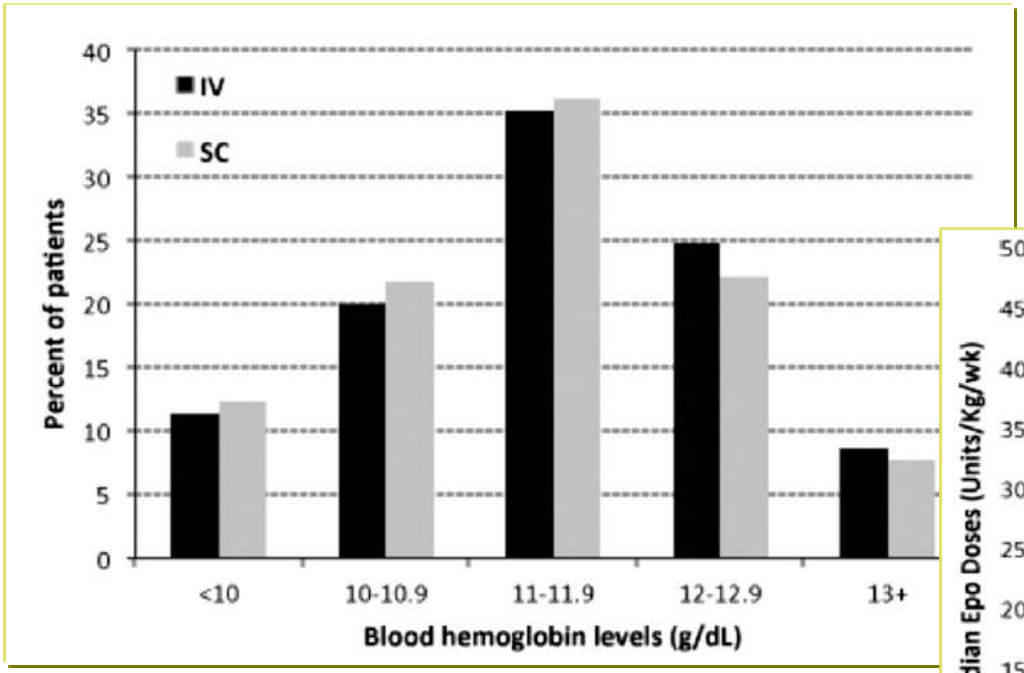
CJASN ePress. Published on September 10, 2015 as doi: 10.2215/CJN.01590215

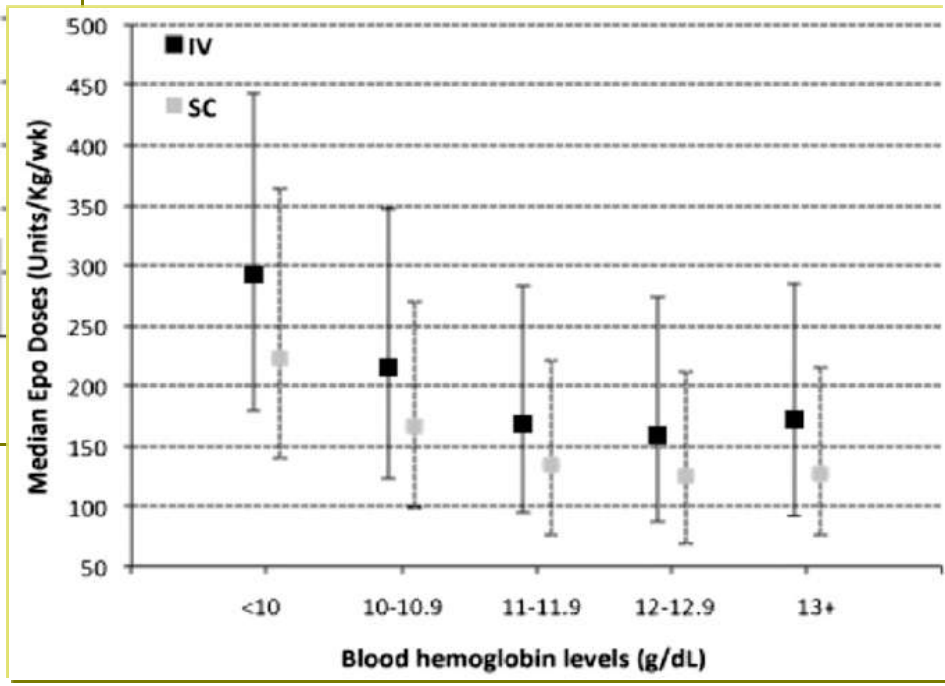
Article

Association of Erythropoietin Dose and Route of Administration with Clinical Outcomes for Patients on Hemodialysis in the United States

Daniel G. Wright, Elizabeth C. Wright,† Andrew S. Narva,‡ Constance T. Noguchi,* and Paul W. Eggers‡*

ESA Route:
Outcome





Clin J Am Society of Nephrology 2015, in Press

ESA Route: Outcome

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Demographic and Clinical Variables of Study Patients	12-mo Composite Events AHR (95% CI)[d]	24-mo Composite Events AHR (95% CI)[d]
All subjects		
Intravenous versus subcutaneous epoetin	1.11 (1.04 to 1.18)	1.09 (1.04 to 1.14)
Men versus women	1.03 (1.00 to 1.07)	1.03 (1.01 to 1.06)
Black versus nonblack race	0.85 (0.82 to 0.88)	0.86 (0.83 to 0.88)
Hispanic versus non-Hispanic	0.91 (0.86 to 0.95)	0.89 (0.85 to 0.92)
Age, yr[a]	1.03 (1.02 to 1.03)	1.03 (1.03 to 1.03)
Dialysis vintage, yr[b]	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
Diabetes mellitus as the cause of ESRD	1.21 (1.18 to 1.25)	1.26 (1.22 to 1.29)
Previous AMI, CHF, or stroke	1.89 (1.83 to 1.96)	1.78 (1.73 to 1.82)
BMI≥25 versus <25	0.82 (0.79 to 0.84)	0.85 (0.82 to 0.87)
Hemoglobin ≤11.5 g/dl	1.21 (1.18 to 1.25)	1.17 (1.14 to 1.20)
Serum albumin ≥3.5/3.2 g/dl[c]	0.65 (0.63 to 0.67)	0.69 (0.67 to 0.71)
Epoetin dose 150–299 versus <150 units/kg per week	1.18 (1.14 to 1.23)	1.15 (1.12 to 1.19)
Epoetin dose ≥300 versus <150 units/kg per week	1.51 (1.46 to 1.57)	1.44 (1.40 to 1.49)
Facility: nonprofit	0.93 (0.89 to 0.98)	0.93 (0.89 to 0.96)
Facility: hospital based	0.87 (0.82 to 0.92)	0.87 (0.83 to 0.92)
Facility: chain affiliated	1.04 (1.00 to 1.07)	0.99 (0.96 to 1.02)
Facility: <20 stations	1.00 (0.97 to 1.03)	1.01 (0.98 to 1.03)
AHR for intravenous versus subcutaneous epoetin by dose level		
Intravenous versus subcutaneous (<150 units/kg per week)	1.12 (1.02 to 1.22)	1.11 (1.03 to 1.19)
Intravenous versus subcutaneous (150–299 units/kg per week)	1.13 (1.01 to 1.25)	1.09 (1.00 to 1.18)
Intravenous versus subcutaneous (≥300 units/kg per week)	1.06 (0.94 to 1.20)	1.04 (0.94 to 1.15)
AHR for intravenous versus subcutaneous epoetin by hemoglobin level		
Intravenous versus subcutaneous (hemoglobin ≤11.5 g/dl)	1.08 (1.00 to 1.17)	1.06 (1.00 to 1.13)
Intravenous versus subcutaneous (hemoglobin >11.5 g/dl)	1.15 (1.05 to 1.26)	1.12 (1.05 to 1.20)

Clin J Am Society of Nephrology 2015, in Press

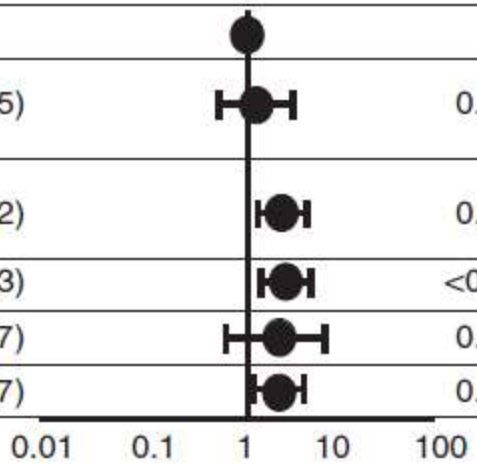
ESA Dose and Outcome: n 1086 HD patients

Urology and Nephrology Center

Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients

Takahiro Kuragano[1], Osamu Matsumura[2], Akihiko Matsuda[3], Taiga Hara[4], Hideyasu Kiyomoto[5], Toshiaki Murata[6], Kenichiro Kitamura[7], Shouichi Fujimoto[8], Hiroki Hase[9], Nobuhiko Joki[9], Atushi Fukatsu[10], Toru Inoue[11], Ikuhiro Itakura[12] and Takeshi Nakanishi[1]

Event	Dose of ESA	Hazard ratio	(95% CI)	*P*-value
	Low dose	1		
Cerebro-cardio-vascular disease	High dose	1.59 (0.88–2.85)		0.122
Infectious disease	High dose	1.48 (1.08–2.02)		0.015
Hospitalization	High dose	1.8 (1.33–2.43)		<0.001
Death	High dose	1.71 (0.48–6.07)		0.407
All events	High dose	1.48 (1.17–1.87)		0.001

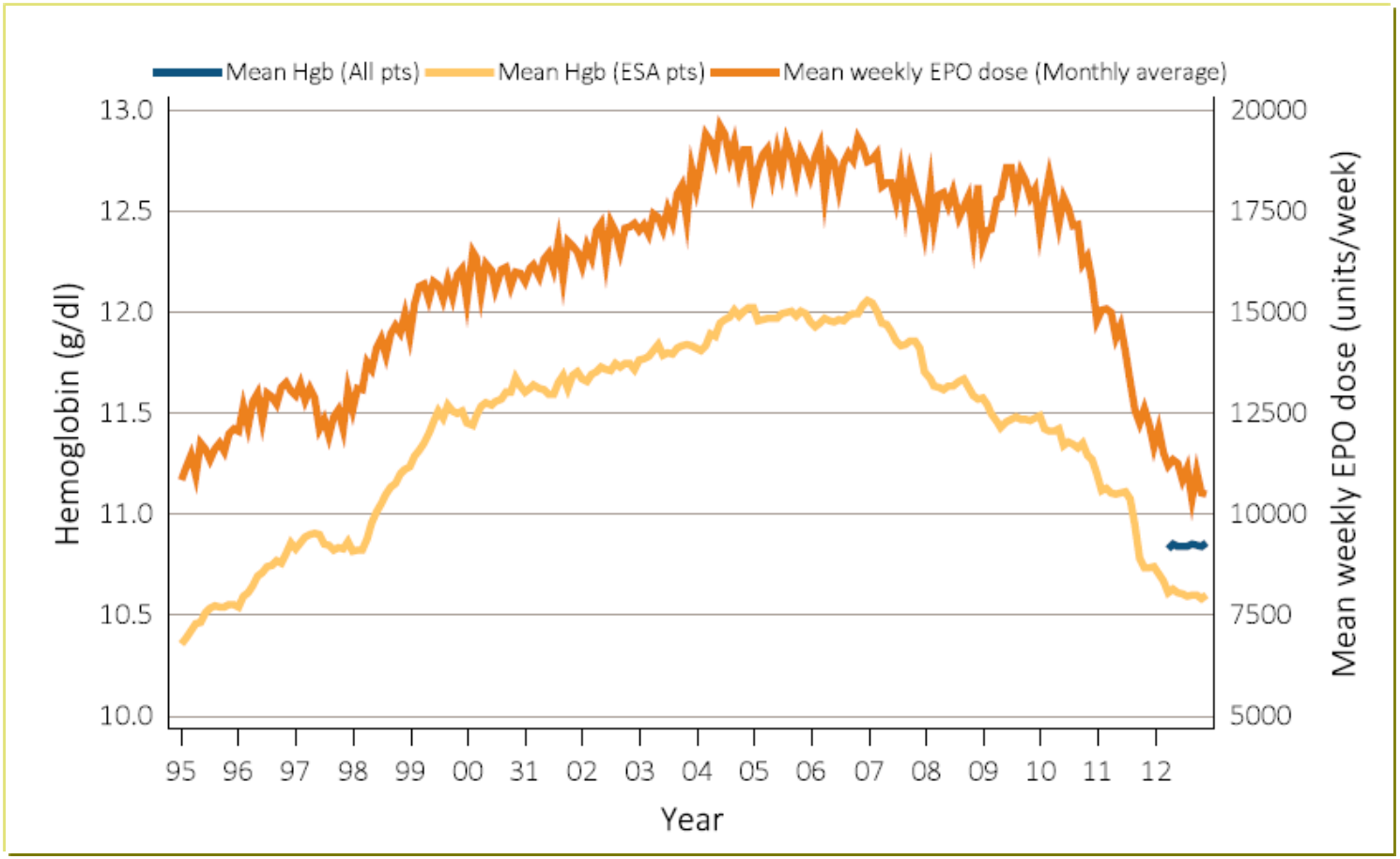


Kidney International (2014) 86, 845–854

Urology and Nephrology Center

Hemoglobin Target

Anemia Management:
USA

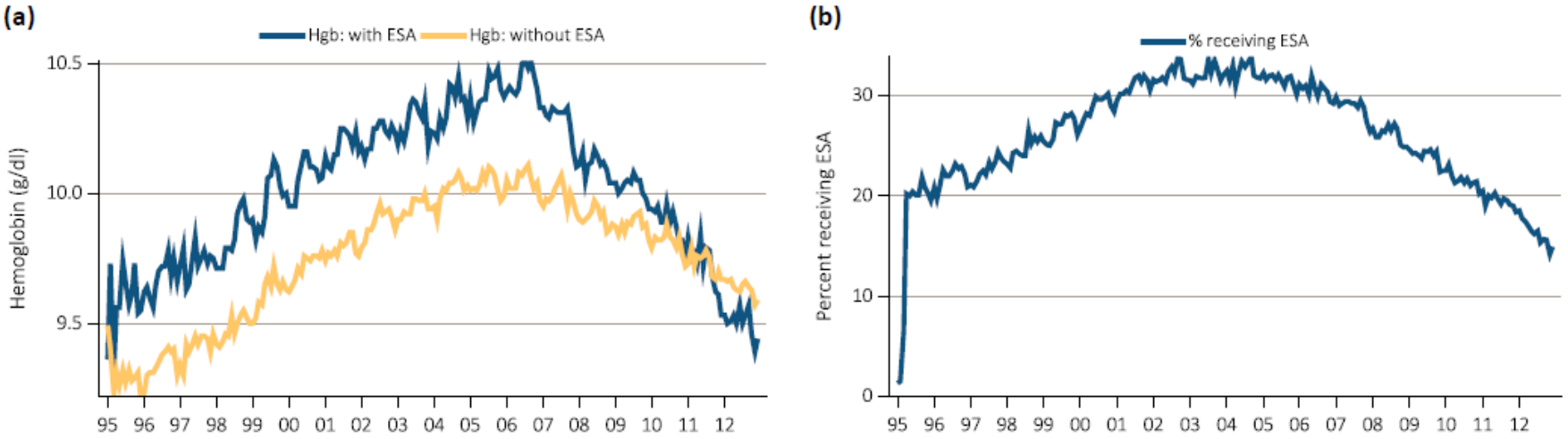


2014 USRDS

Anemia Management:
USA (Pre-ESRD)

Urology and Nephrology Center

vol 2 **Figure 1.21 Trend in (a) Hgb levels and (b) the percentage of patients who received pre-ESRD erythropoiesis-stimulating agent (ESA) treatment, among incident ESRD patients, 1995-2012**



Data Source: Special analyses, USRDS ESRD Database. Abbreviations: ESA, erythropoiesis-stimulating agents; ESRD, end-stage renal disease.

2014 USRDS

Anemia Management:
Hemoglobin Target

Anemia Management:

ESA if Hb<11 in ND or <10 in DP

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nephron Clinical Practice

Clinical Practice: Second Opinion

Nephron
DOI: 10.1159/000440849

Received: May 9, 2015
Accepted: September 1, 2015
Published online: September 19, 2015

How the Target Hemoglobin of Renal Anemia Should Be?

Imari Mimura Tetsuhiro Tanaka Masaomi Nangaku

Division of Nephrology and Endocrinology, The University of Tokyo, Tokyo, Japan

Urology and Nephrology Center

How to Reduce The Cost

ESA Therapy:
How to Reduce The Cost

Urology and Nephrology Center

Original Paper

nephron Clinical Practice

Nephron Clin Pract 2005;99:c102–c106
DOI: 10.1159/000083891

Received: April 6, 2004
Accepted: November 18, 2004
Published online: February 8, 2005

Use of Nandrolone Decanoate as an Adjuvant for Erythropoietin Dose Reduction in Treating Anemia in Patients on Hemodialysis

A Prospective Randomized Controlled Study

Hussein Sheashaa[a] Waleed Abdel-Razek[a] Amr El-Husseini[a] Amal Selim[b]
Nabil Hassan[a] Tarek Abbas[a] Hassan El-Askalani[c] Mohamed Sobh[a]

[a]Nephrology Unit, Urology and Nephrology Center; [b]Medical Biochemistry Department, and [c]Internal Medicine Department, Mansoura University, Mansoura, Egypt

ESA Therapy:
How to Reduce The Cost

Urology and Nephrology Center

Original Paper

nephron Clinical Practice

Nephron Clin Pract 2005;99:c97–c101
DOI: 10.1159/000083766

Received: January 9, 2004
Accepted: May 26, 2004
Published online: February 3, 2005

Parenteral Iron Therapy in Treatment of Anemia in End-Stage Renal Disease Patients: A Comparative Study between Iron Saccharate and Gluconate

Hussein Sheashaa Amr El-Husseini Alaa Sabry Nabil Hassan
Ayman Salem Abdalla Khalil Amgad El-Agroudy Mohamed Sobh

Nephrology Unit, Urology and Nephrology Center, Mansoura University, Mansoura, Egypt

ESA Therapy:
How to Reduce The Cost

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RCT 411 (FC: Active control)

Saving 2101 USD/P/Y

Drugs R D (2015) 15:271–279
DOI 10.1007/s40268-015-0103-y

CrossMark

ORIGINAL RESEARCH ARTICLE

Ferric Citrate, an Iron-Based Phosphate Binder, Reduces Health Care Costs in Patients on Dialysis Based on Randomized Clinical Trial Data

Roger A. Rodby[1,6] · Kausik Umanath[2] · Robert Niecestro[3] · T. Christopher Bond[4] · Mohammed Sika[5] · Julia Lewis[5] · Jamie P. Dwyer[5] · For the Collaborative Study Group

Published online: 4 August 2015

ESA Therapy:
How to Reduce The Cost

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RCT-DB, n 103 HD patients

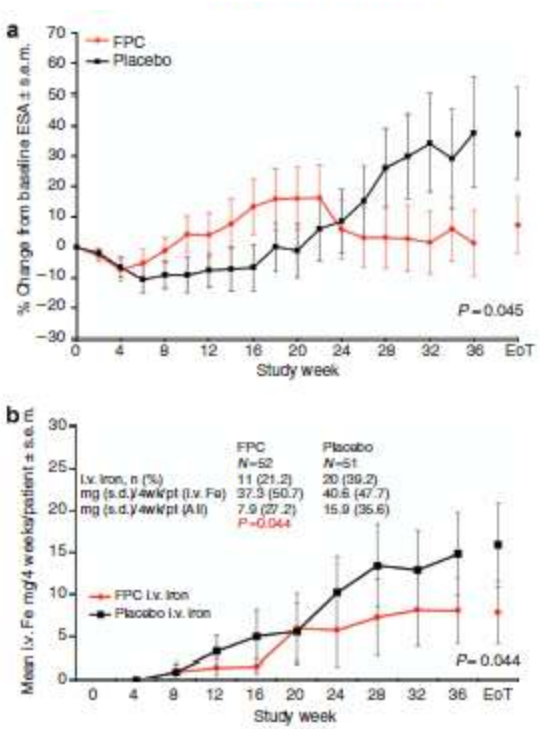
http://www.kidney-international.org

OPEN

Ferric pyrophosphate citrate adminis dialysate reduces erythropoiesis-stim use and maintains hemoglobin in he patients

Ajay Gupta[1,2], Vivian Lin[2], Carrie Guss[2], Raymond Pratt[2], T. Alp Ikizler[3] and

[1]Division of Nephrology, University of California, Irvine, California, USA; [2]Rockwell Medical, Wi [3]Department of Medicine, Division of Nephrology and Hypertension, Vanderbilt University, Na of Nephrology, Department of Medicine, Stanford University, Palo Alto, California, USA and [5]U California, USA



Kidney International advance online publication, 8 July 2015;

Pentoxifylline:

11 studies/ 377 Patients

RESEARCH ARTICLE

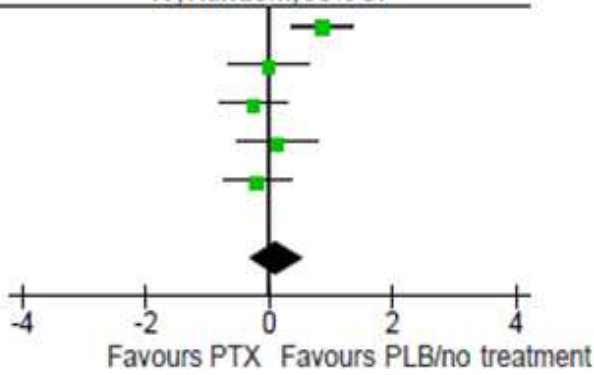
Pentoxifylline for Anemia in Chronic Kidney Disease: A Systematic Review and Meta-Analysis

ESAs dosage

Study	Pentoxifylline Mean	SD	Total	PLB/no treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Antunes 2013	11,000	1,154.7	35	10,000	1,155	36	22.2%	0.86 [0.37, 1.34]
Gonzalez-Espinoza 2012	40	17.3	18	40	17.3	18	18.3%	0.00 [-0.65, 0.65]
HERO 2015	236.4	117.6	24	268.2	122.6	26	20.5%	-0.26 [-0.82, 0.30]
Mora-Gutierrez 2013	106.1	89.7	18	96.4	33.5	18	18.3%	0.14 [-0.51, 0.79]
Mortazavi 2012	7.5	4.4	25	8.3	3.4	25	20.6%	-0.20 [-0.76, 0.36]
Total (95% CI)			120			123	100.0%	0.12 [-0.32, 0.57]

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 11.88$, df = 4 (P = 0.02); $I^2 = 66\%$

Test for overall effect: Z = 0.54 (P = 0.59)



PLOS ONE | DOI:10.1371/journal.pone.0134104 August 3, 2015

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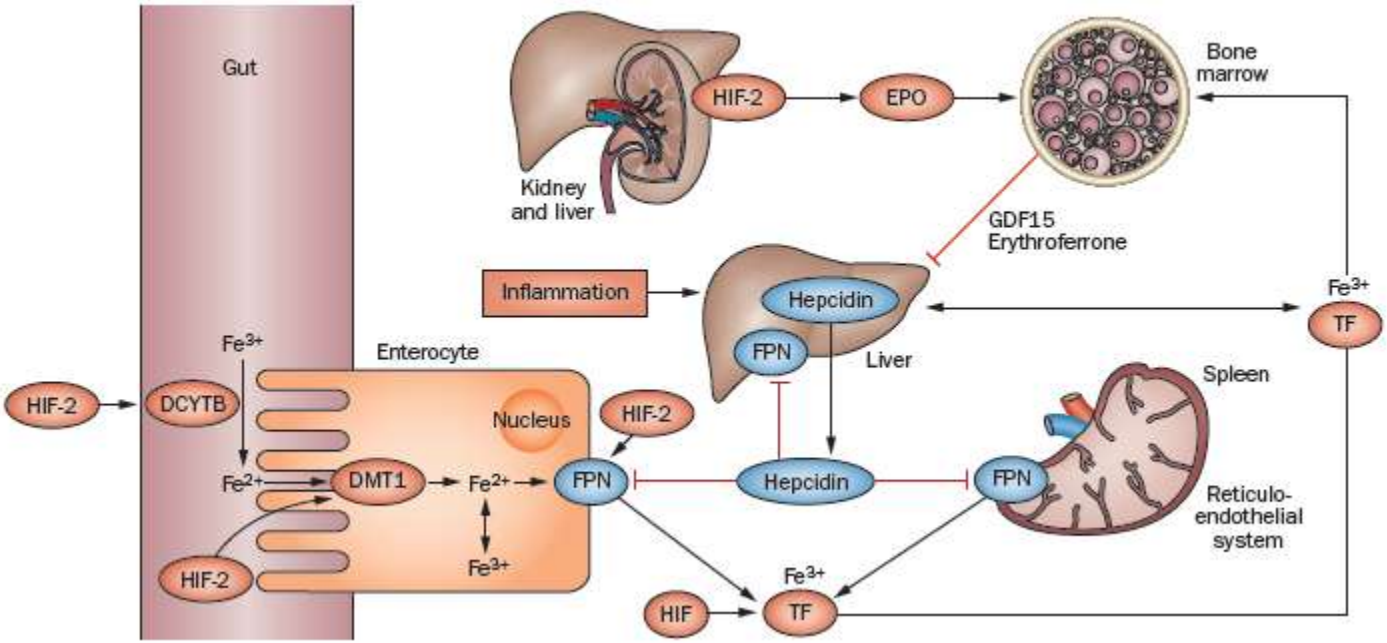
DNG

ESA Therapy and Hypoxia

Anemia Control:
Effect of Hypoxia



Nat. Rev. Nephrol. 11, 394–410 (2015); published online 9 June 2015

Anemia Control: Effect of Hypoxia

Urology and Nephrology Center

Hypoxia-Inducible Factor Stabilizers Under Clinical Development

Drug	Company	Stage of Clinical Development
FG-4592 (Roxadustat)	Fibrogen[a]	Phase 2 studies completed (NDD CKD, HD, PD); phase 3 studies ongoing (NDD CKD, HD, PD)
AKB-6548	Akebia Therapeutics	Phase 2 studies completed (NDD CKD) or ongoing but not recruiting (HD)
GSK1278863	Glaxo Smith Kline	Phase 2a studies completed (NDD-CKD, HD); phase 2b studies ongoing, but not recruiting (NDD CKD)
BAY 85-3934 (Molidustat)	Bayer Pharmaceuticals	Phase 2b studies ongoing (NDD CKD, HD)
JTZ-951	Akros Pharmaceuticals	Phase 1 study completed (HD)
DS-1093a	Daiichi Sankyo	Phase 1 study ongoing (CKD 3b-4)

Abbreviations: CKD, chronic kidney disease; HD, hemodialysis; NDD, non–dialysis-dependent; PD, peritoneal dialysis.
[a]Collaboration with Astra Zeneca in the United States and China and with Astellas Pharma for Europe, Japan, the Middle East, and South Africa.

Am J Kidney Dis. 2015; in press

Anemia Control: Effect of Hypoxia

Urology and Nephrology Center

96/116 p ND-CKD, FG-4592/placebo (3:1)

NDT Advance Access published August 20, 2015

Nephrol Dial Transplant (2015) 0: 1–9
doi: 10.1093/ndt/gfv302

ndt Nephrology Dialysis Transplantation

FASTTRACK *Original Article*

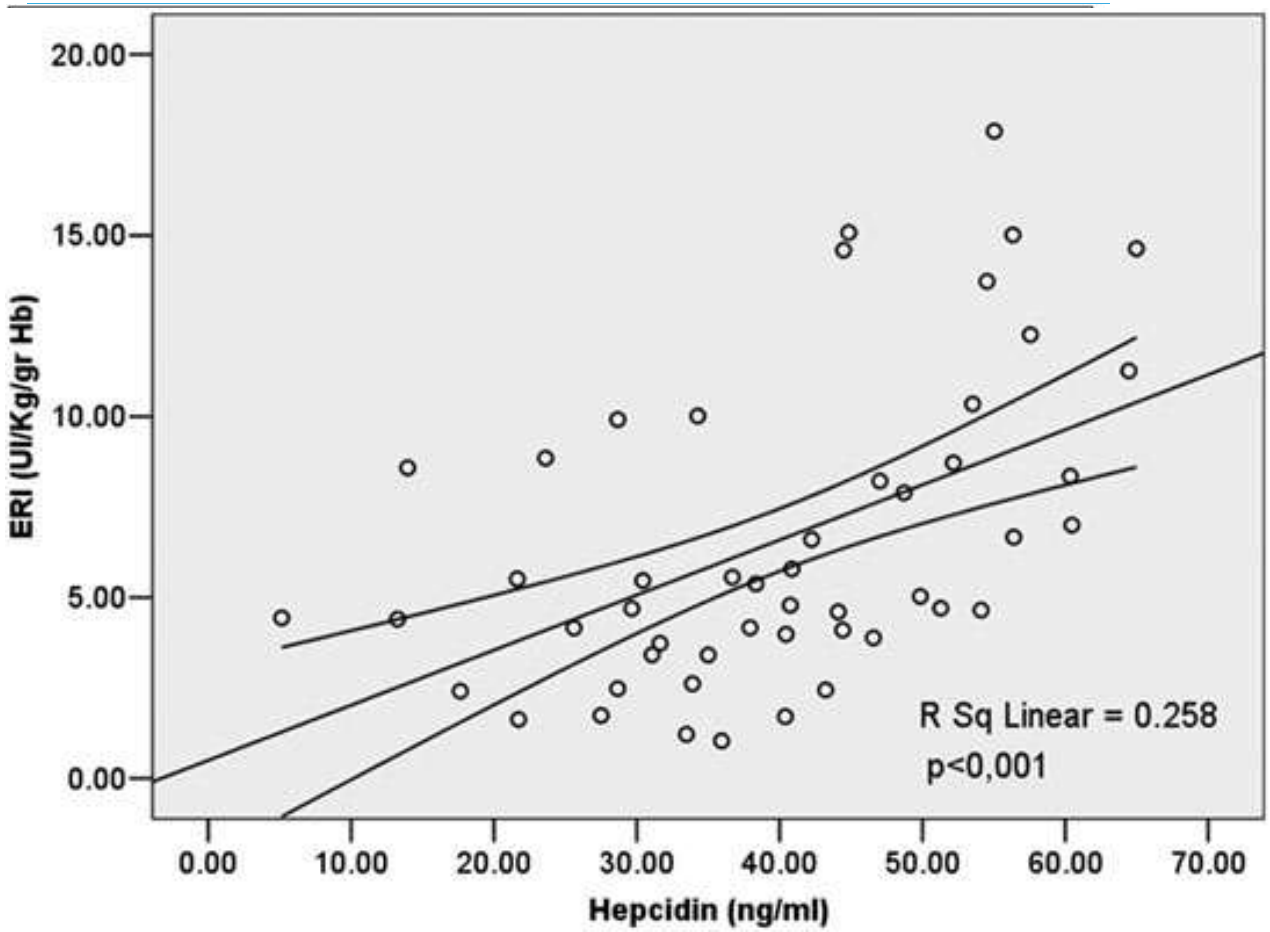
Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

Anatole Besarab[1], Robert Provenzano[2], Joachim Hertel[3], Raja Zabaneh[4], Stephen J. Klaus[1], Tyson Lee[1], Robert Leong[1], Stefan Hemmerich[1], Kin-Hung Peony Yu[1] and Thomas B. Neff[1]

[1]FibroGen, Inc., San Francisco, CA, USA, [2]St Clair Specialty Physicians, Detroit, MI, USA, [3]Kidney Care Associates, LLC, Augusta, GA, USA and [4]Northwest Louisiana Nephrology, Shreveport, LA, USA

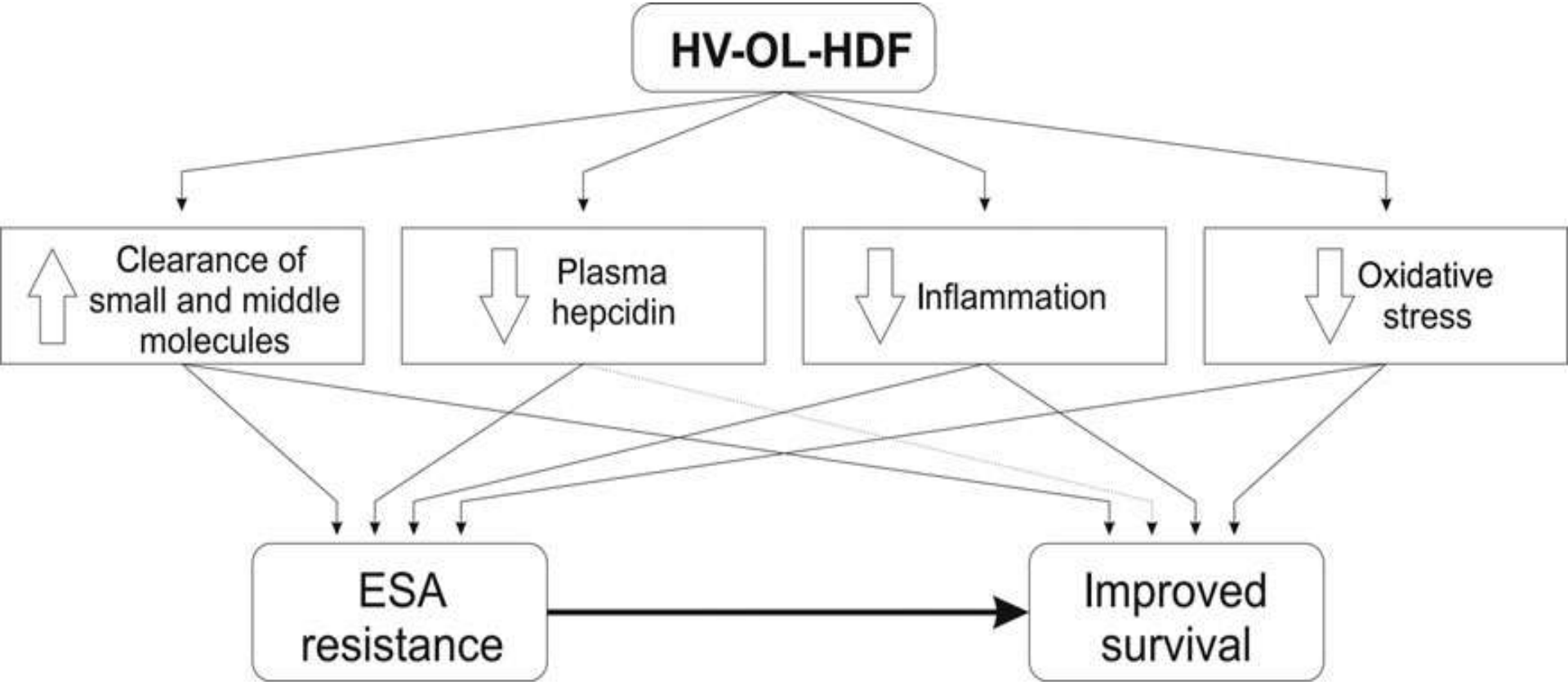
ESA Therapy and HD Modality

ESA Response and HDF



Nephrol Dial Transplant (2015) 30: 682–689

ESA Response and HDF



Nephrol Dial Transplant (2015) 30: 523–525

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DNG

ESA Therapy and PRCA

ESA Therapy:
Pure Red Cell Aplasia

Urology and Nephrology Center

Hindawi Publishing Corporation
Case Reports in Transplantation
Volume 2015, Article ID 286276, 5 pages
http://dx.doi.org/10.1155/2015/286276

Case Report

Anti-Erythropoietin Antibody Associated Pure Red Cell Aplasia Resolved after Liver Transplantation

Annie K. Hung,[1] Jennifer Guy,[2] Caroline M. Behler,[3] and Eugene E. Lee[1]

[1]*Department of Internal Medicine, California Pacific Medical Center, San Francisco, CA 94115, USA*
[2]*Department of Hepatology, California Pacific Medical Center, San Francisco, CA 94115, USA*
[3]*Department of Hematology Oncology, California Pacific Medical Center, San Francisco, CA 94115, USA*

ESA Therapy:
Pure Red Cell Aplasia

CEN Case Rep
DOI 10.1007/s13730-015-0196-8

CASE REPORT

Successful treatment of a hemodialyzed patient with pure red cell aplasia associated with epoetin beta pegol therapy with cyclosporine

Keiji Hirai[1] · Susumu Ookawara[1] · Haruhisa Miyazawa[1] · Kiyonori Ito[1] · Yuichiro Ueda[1] · Yoshio Kaku[1] · Taro Hoshino[1] · Shun-ichi Kimura[2] · Izumi Yoshida[1] · Sachiko Kakuta[3] · Yoshiyuki Morishita[1] · Kaoru Tabei[1]

ESA Therapy and Cancer

ESA Therapy and Chemotherapy Associated Anemia

EPIDEMIOLO

The effects -term
and long-t s
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Yinzhi Lai[1] · Zh
Zhaomei Mu[3] · I
Hushan Yang[1]

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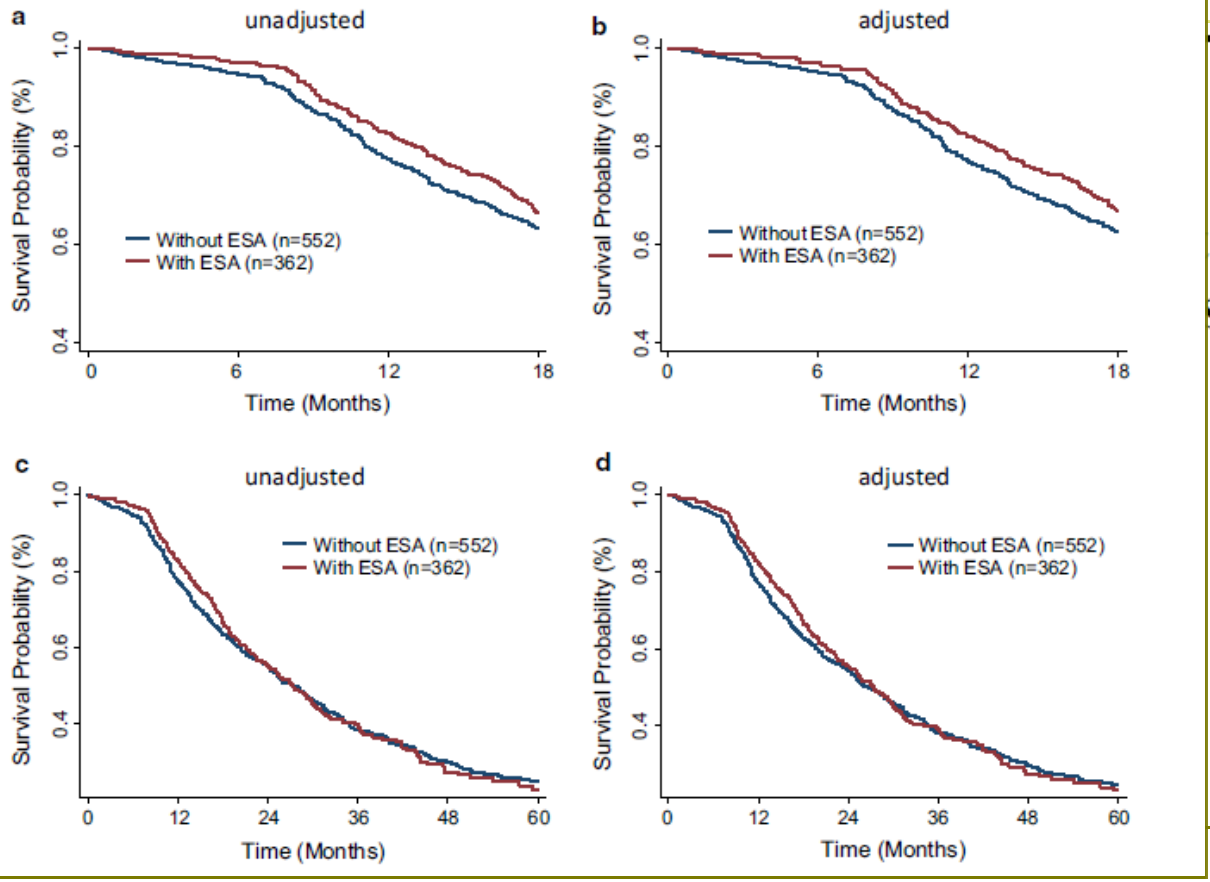

Breast Cancer Res Treat (2015) 153:407–416

Urology and Nephrology Center

ESA Therapy and Progression of CKD

Anemia Control:
Effect on CKD Progression

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Original Article

Complications

Diabetes Metab J 2015;39:240-246
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dmj

DIABETES & METABOLISM JOURNAL

n130 T2DN Korean

The Relationship between Anemia and the Initiation of Dialysis in Patients with Type 2 Diabetic Nephropathy

Sun Hee Kim, Kyung

Division of Endocrinology
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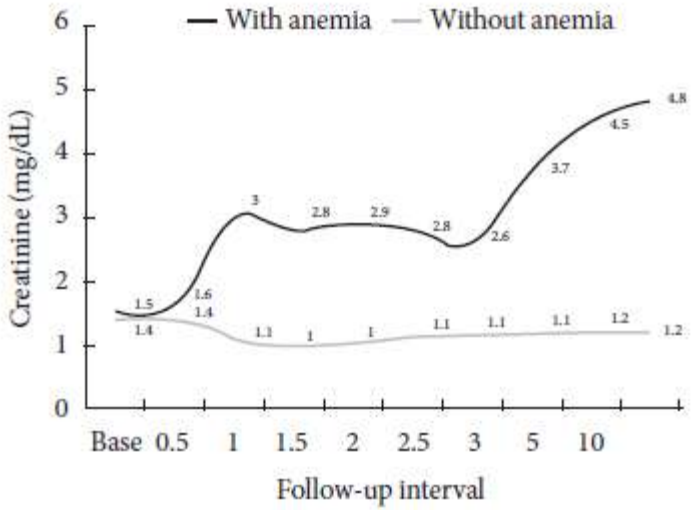
nbuk National University-Chonbuk



Anemia Control:
Effect on CKD Progression

Urology and Nephrology Center

N297 CKD

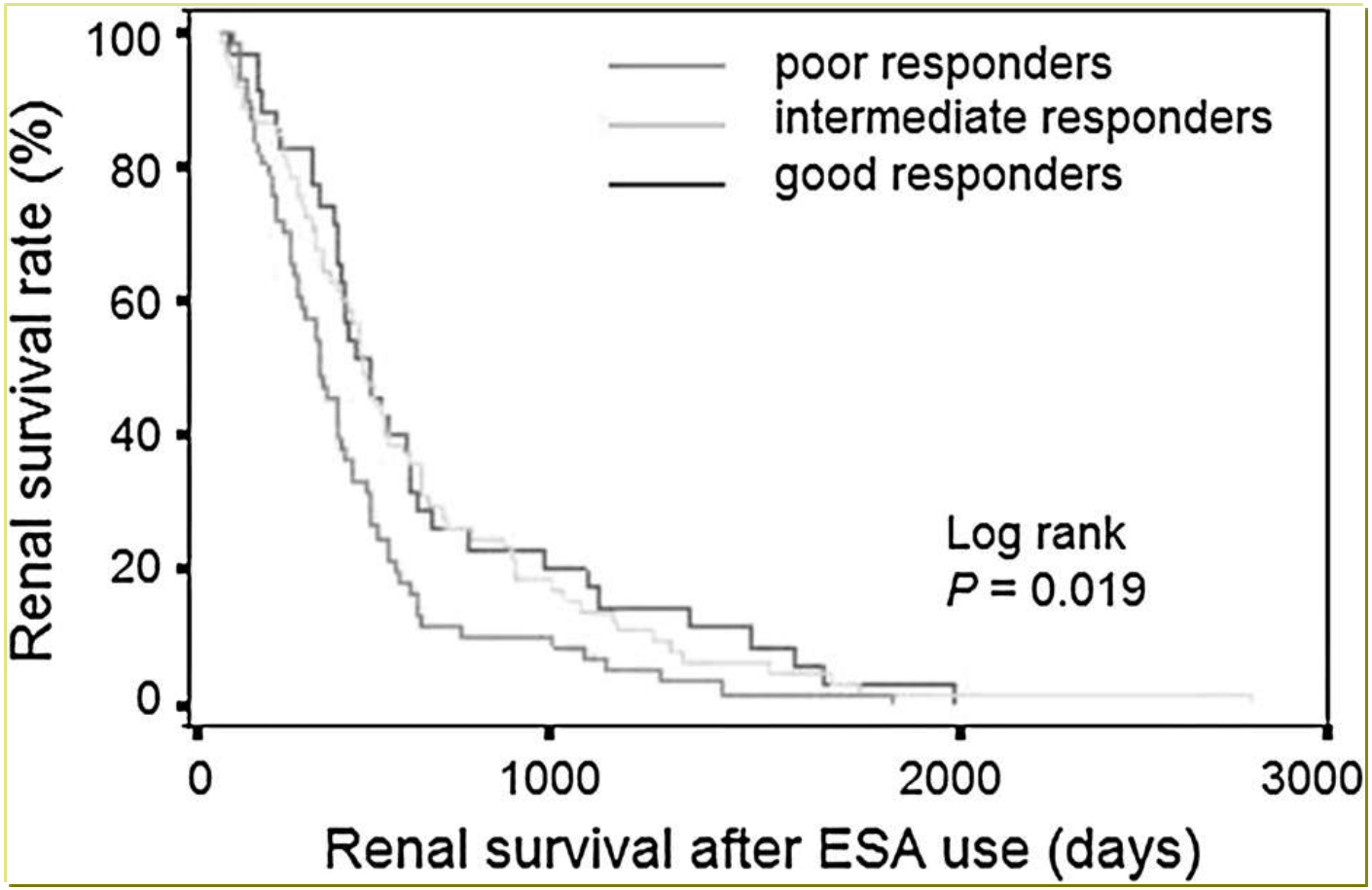
ORIGINAL ARTICLE

Responsiveness to erythropoiesis-stimulating agents and renal survival in patients with chronic kidney disease

Michio Kuwahara · Shintaro Mandai · Yuri Kasagi · Keita Kusaka · Tomomi Tanaka · Satomi Shikuma · Wataru Akita

Clin Exp Nephrol (2015) 19:598–605

Anemia Control:
Effect on CKD Progression



Clin Exp Nephrol (2015) 19:598–605

Anemia Control:
Effect on CKD Progression

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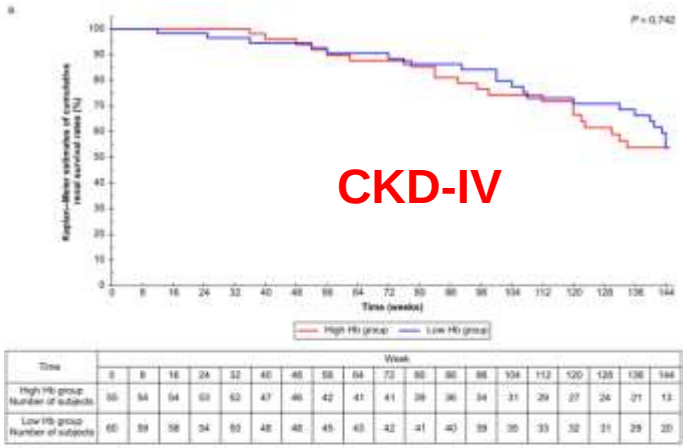
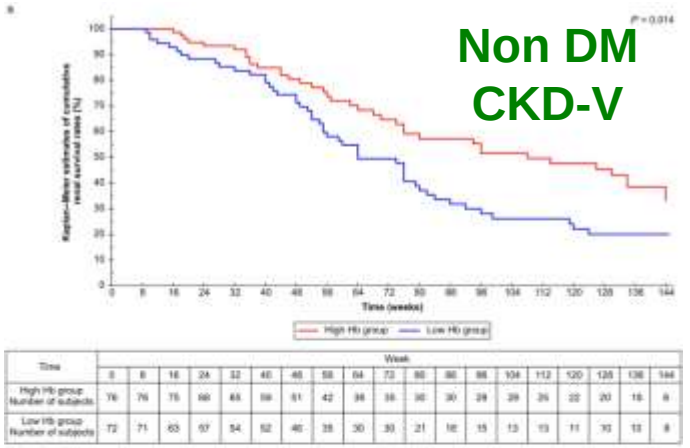
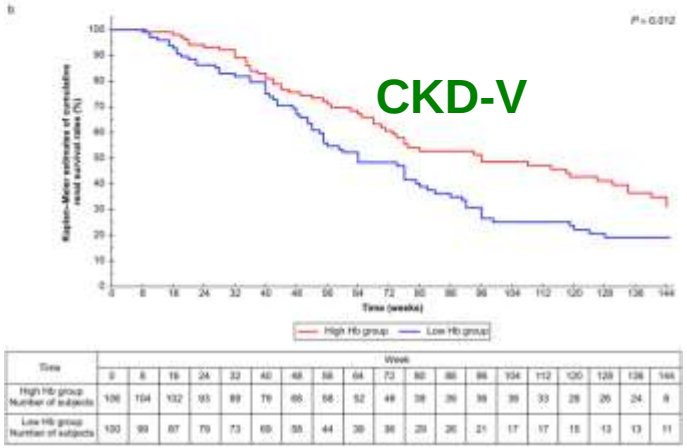
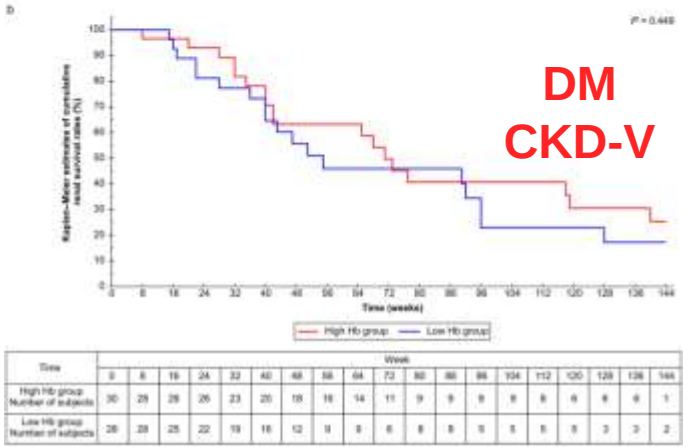
From RCT, 321 ND-CKD









Therapeutic Apheresis and Dialysis 2015; in press

Anemia Control: Effect on CKD Progression

Urology and Nephrology Center

PREDICT (Enrolled 498 non DM- CKD)

Clin Exp Nephrol
DOI 10.1007/s10157-015-1133-z

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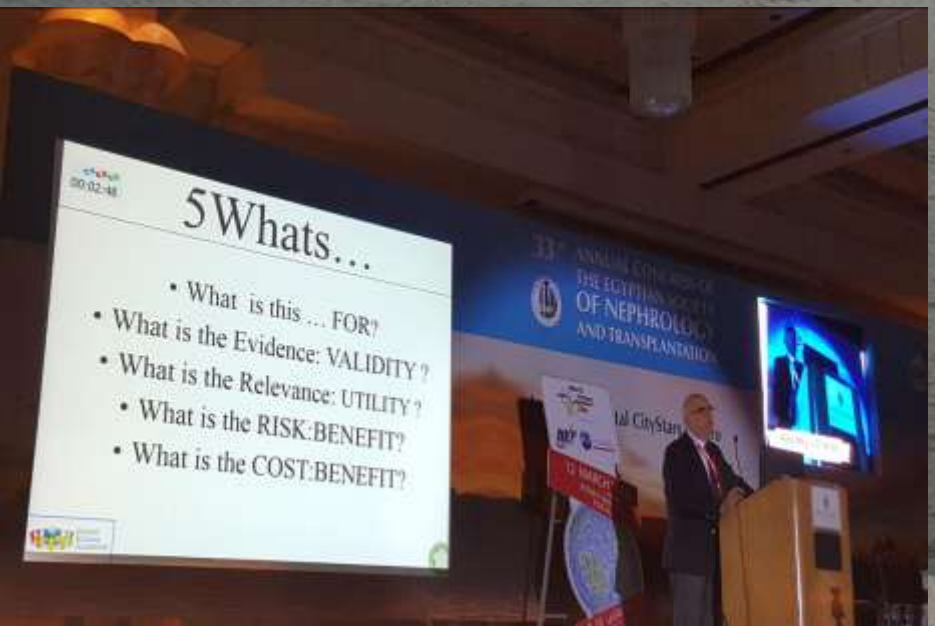
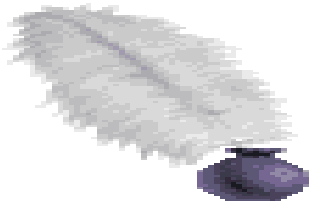
ORIGINAL ARTICLE

Rationale and study design of a randomized controlled trial to assess the effects of maintaining hemoglobin levels using darbepoetin alfa on prevention of development of end-stage kidney disease in non-diabetic CKD patients (PREDICT Trial)

Enyu Imai[1,2] · Shoichi Maruyama[3] · Masaomi Nangaku[4] · Hideki Hirakata[5] · Terumasa Hayashi[6] · Ichiei Narita[7] · Hideki Kono[8] · Eiji Nakatani[8] · Satoshi Morita[9] · Yoshiharu Tsubakihara[10] · Tadao Akizawa[11]


5Whats…
• What is this … FOR?
• What is the Evidence: VALIDITY?
• What is the Relevance: UTILITY?
• What is the RISK:BENEFIT?
• What is the COST:BENEFIT?



- إنَّ الطَّبيبَ بِطبِّهِ ودَوائِهِ لا يَستطيع دِفَاعَ مَكروهٍ أتى
- ما للطبيبِ يَموتُ بالدَّاءِ الذي قَد كَان يُبْرئُ منه فيما قد مضى
- ذَهَبَ الـمُدَاوِي والـمُدَاوَى والذي جَلَبَ الدَّواءَ وبَاعه ومَنِ اشترى